

## **Amendment to the Specification**

Please replace paragraph 1 on p. 1, under the heading "Related Applications", with the following paragraph:

This application claims priority to, and the benefit of PCT/US99/28592, filed on December 1, 1999, which claims priority to, and the benefit of USSN 60/110,616, filed on December 2, 1998, the disclosures of which are incorporated by reference herein. Related applications include: USSN 09/872,868 (~~Attorney Docket No. CEL-002~~), filed June 1, 2001 and USSN 09/872,338 (~~Attorney Docket No. CEL-004~~), filed June 1, 2001 the disclosures of which are incorporated by reference herein.

Please replace the paragraph bridging pages 6 and 7 with the following paragraph:

Accordingly, unlike a toggle switch construct (see USSN 09/872,868, ~~Attorney Docket No. CEL-002~~ and PCT/US/28592) in which transcription from either promoter is equally stable, an adjustable-threshold switch construct has a "default" transcription state in which transcription of genes from the first promoter is, for example, "off" while that from the second promoter is "on". The default transcription of the gene of interest may be manipulated such that it is in a default "off" or "on" state by inserting the gene of interest downstream of either of the first or second promoter, respectively. An adjustable-threshold system of the invention is able to transition sharply from ~~transcription~~ a first transcription state (*e.g.*, suppression of  $R_1$  and transcription of  $R_2$ ) to a second transcription state (*e.g.*, transcription of  $R_1$  and suppression of  $R_2$ ) by the application of the activating agent at a concentration that exceeds a desired threshold concentration. This sharp switching is also exemplified by the similar toggle switch constructs described in PCT/US99/28592.

Please replace the paragraph bridging pages 33 and 34, under the heading "Example 4. Design and Construction of a Plasmid Carrying an Exemplary Adjustable-Threshold Switch" with the following paragraph:

The experimental methods used to construct and test adjustable-threshold switch constructs are similar to those discussed for the toggle switch constructs described in USSN 09/872,868 [~~Attorney Docket No. CEL-002~~]. It is contemplated that elements of an adjustable-threshold switch construct may be arranged in the same configuration as those in the toggle switch construct except that one of the constitutive promoters is replaced by a promoter ~~that is activatable~~ from which transcription can be activated by an activating agent (see Figure 10A). Additionally, expression from this promoter is preferably negligible in the absence of an activating agent. Finally, this promoter is preferably simultaneously suppressed by the opposing gene in the switch construct (*i.e.*, regulatory gene 2 ( $R_2$ ) in Figures 1A and 1B). Construction of a promoter that satisfies all of the above requirements is facilitated by the modular structure of the  $P_{trc}$  promoter used in Example 1. The Lac repressor binding site begins at the first nucleotide of the mRNA transcript. The complete  $P_{trc}$  promoter, including all of the RNAP recognition sites, is located upstream of the Lac repressor binding site. Thus, the entire  $P_{trc}$  promoter upstream of the +1 nucleotide may be removed and replaced by nearly any positively regulated promoter element, such as the promoters set forth in Table 2. The new hybrid promoter, which retains the Lac repressor binding site, is thus both positively and negatively regulated. For example, the  $P_{bad}$  promoter, which is activated by the AraC protein in the presence of arabinose, is fused to the  $O_{lac}$  operator region of  $P_{trc}$  (Figure 10B, and SEQ ID NO: 12). The resulting hybrid promoter is positively activated by AraC-arabinose and repressed by lacI (Figure 10A).